UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MINNESOTA

IN RE:	MDL DOCKET NO. 1724
VIAGRA PRODUCTS LIABILITY LITIGATION	Judge Paul A. Magnuson
This Document Relates To: ***Martin v. Pfizer Inc.*, 06-cv-1064**	

EXPERT REPORT OF SIMMONS LESSELL, MD
RE: RICHARD MARTIN

EXPERT REPORT OF SIMMONS LESSELL, MD, RE: RICHARD MARTIN

Qualifications

1. I am the Paul Austin Chandler Professor of Ophthalmology at Harvard Medical School and am Surgeon in Ophthalmology at the Massachusetts Eye and Ear Infirmary. I was the Director of Neuro-Ophthalmology at the Massachusetts Eye and Ear Infirmary from 1984-2005.

2. I received my medical degree from Cornell University Medical College in 1958. Following internship in Internal Medicine I was a resident in Neurology at the University of Vermont. Following a year of Neurology residency I became a commissioned officer in the U.S. Public Health Service. My appointment was to the Epidemiology and Genetics branch of the National Institute of Neurological Diseases and Blindness. I completed the Epidemic Intelligence Service course in Chamblee Georgia. My research was mainly on the epidemiology of Lou Gehrig's disease (amyotrophic lateral sclerosis) and related neurological diseases in the Marianas Islands where I spent 13 months. During that time I was also the only neurologist for approximately 30,000 civilians and 30,000 military personnel. I was then a fellow at Harvard's Howe Laboratory of Ophthalmology where I performed laboratory research on the retina and optic nerve. Following that I completed a residency in Ophthalmology at the Massachusetts Eye and Ear Infirmary.

3. My board certification in Ophthalmology was in 1967. There is no board examination, qualifying or certifying examination in Neuro-Ophthalmology. Immediately upon completion of my residency I was appointed Associate Professor of Ophthalmology at Boston University where I rose to the rank of Professor of Ophthalmology, Neurology and Anatomy. Supported by grants from the National

Institute of Neurological Diseases and Blindness (later the National Eye Institute) I was the principle investigator of a research laboratory investigating toxic disorders of the retina and optic nerve. I was concurrently an active neuro-ophthalmic clinician primarily evaluating and treating patients sent for consultation.

4. In 1984 I was appointed Professor of Ophthalmology at Harvard Medical School where I am the Paul Austin Chandler Professor of Ophthalmology. I directed the Neuro-Ophthalmology Unit of the Massachusetts Eye and Ear Infirmary until I relinquished that position in 2005. Currently, in addition to teaching, I maintain an active neuro-ophthalmic practice with a special emphasis on diseases of the optic nerve. I am on the editorial board of the Archives of Ophthalmology and the Journal of Neuro-Ophthalmology; I also am the co-editor of the Neuro-Ophthalmology section of the leading textbook in Ophthalmology (Albert & Jakobiec, Principals and Practice of Ophthalmology). Further biographic information, including a list of my publications and editorial responsibilities, is set forth in the appended curriculum vitae.

5. I have been asked by Pfizer to review the case of Mr. Richard Martin and to consider whether Viagra (sildenafil) caused or contributed to his development of an ocular disorder, called non-arteritic anterior ischemic optic neuropathy (NAION). In considering this question, I have reviewed the pertinent medical records regarding Mr. Martin; the deposition testimony of Mr. Martin, his spouse and his treating physicians; the medical literature on NAION and Viagra, including the articles cited herein; a report submitted by Pfizer's expert epidemiologist, Stephen E. Kimmel, MD; and the reports submitted by plaintiffs' experts. A bibliography of references is attached. I am also relying on my medical training and experience as a neuro-ophthalmologist.

All of my opinions contained herein are held to a reasonable degree of medical certainty.

Background

6. The process of "seeing" is complex and only begins with the eye. In order to be perceived, the visual information imprinted on the retina of the eye must be transmitted from the eyeball to the areas of the brain that process vision. The optic nerve is the structure that conveys this visual information from the eye to the brain. Each optic nerve can be thought of as a cable containing over a million "wires" which are actually the extensions of individual nerve cells. The beginning, or most anterior portion, of the optic nerve (referred to as the optic disc or optic nerve head) is literally within the eyeball and therefore is visible to the physician when the eye is examined with an appropriate instrument.

7. *Optic neuropathy* is the general term that designates the presence of a disorder of the optic nerve. *Ischemic* refers to the situation in which there is a reduction in the delivery of blood to a structure. *Inflammation* is a term that designates structures with several or all of the following features: pain, redness, tenderness to touch, heat, swelling and impaired function. Arthritis, in which a joint has become inflamed, is a common example of inflammation. *Arteritic and non-arteritic* are terms that refer respectively to inflamed structures and non-inflamed structures.

8. In the context of Mr. Martin's eye disorder, the terms are applied to the blood vessels that supply the eye and optic nerve. Non-arteritic anterior ischemic optic neuropathy (NAION) is thus a disorder of the optic nerve in which the presumed cause is reduced delivery of blood to the optic nerve head that is not the result of inflammation of the blood vessels that supply the eye or optic nerve. NAION occurs predominantly in individuals whose optic nerve head has a particular configuration such that the surface is

flat or has only a small depression (referred to by ophthalmologists variably as a small or absent physiological cup or a low cup-to-disc ratio). It is an acute disorder that impairs visual function to varying degrees, typically in one eye initially, and causes edema (swelling) of the optic nerve head. The vast majority of cases of NAION are *spontaneous* meaning that the cause is unknown. Spontaneous NAION "is the most common acute optic neuropathy in patients over age 50 years." (Lee, 2005).

Evidence Against Sildenafil Playing A Role In Mr. Richard Martin's NAION

9. As explained later in this document, the scientific evidence does not support the hypothesis that sildenafil has a causal link to NAION in *anyone*. However, even assuming that there were such evidence, is there evidence to support a relation between Mr. Martin's use of the medication sildenafil and his NAION? In my opinion there is no relation between his use of sildenafil and Mr. Martin's attack of NAION for the following reasons:

10. First, Mr. Martin is typical of patients predisposed to spontaneous NAION: an elderly man with high blood pressure (hypertension), evidence of vascular disease, and a small cup-to-disc ratio (as noted above, this configuration of the optic nerve head is prevalent in patients with NAION). (Ischemic Optic Neuropathy Decompression Trial Study Group, 1996). In his case, the evidence of pre-existing vascular disease included narrowing of the carotid artery (the main artery bringing blood from the heart to the brain and eye) and a history of transient ischemic attacks "TIAs." (MARTIN, R FERRERA 0362) A transient ischemic attack is a sudden, brief, temporary episode of neurological dysfunction that often indicates the presence of vascular disease and is frequently a warning of a stroke of the brain or eye. Mr. Martin suffered attacks of NAION in each eye sequentially with acute impairment of visual function and swelling of the optic nerve

head. Involvement of the second eye by NAION is a common occurrence in patients with NAION (Beri, 1987) which can occur "days, months or even years apart." (Hayreh, p. 297, 2005). The clinical symptoms and signs are exactly those that are found in spontaneous cases of NAION. Thus Mr.Martin's personal characteristics and the clinical story are no different from those in spontaneous NAION.

11. Second, Mr. Martin had ingested sildenafil once a week for more than four years prior to the attack of NAION without suffering any undesirable side-effects. That means that the first approximately 200 exposures ("challenges" and "rechallenges") produced no ill-effects.

12. Third, the time interval between Mr. Martin's last use of sildenafil and the onset of his visual impairment is uncertain. This information is critical because the amount of sildenafil remaining in the bloodstream (plasma concentration) is very low 12 hours after the medication has been taken, even in patients 65 years of age or older (Physicians' Desk Reference, p. 2562, 2008). Depending upon which testimony one accepts, Mr. Martin's first attack occurred either when he was not exposed to sildenafil (see Dr. Ferrera's medical records dated October 6, 2004: MARTIN, R FERRERA 0092), or about 24 hours after using it (see Mr. Martin's deposition testimony page 168, lines 16-21). In the former case it is obvious that sildenafil could not have played a role. Even in the latter case, in view of the short half-life of the medication, sildenafil would have been metabolized (degraded by chemical processes in the liver) and no longer present in Mr. Martin's system. In regard to the attack of NAION in his second eye, Mr. Martin in his deposition (pages 172-176) testified that he took the sildenafil around 7-8 PM and that the visual loss occurred at dusk the next day. Even accepting that

testimony at face value, the interval, which I estimate to be no less than 22 hours is, again, such that the sildenafil would have been absent from his body or (less likely) present in such a tiny concentration as to be inconsequential. However, there is also the information that Mr. Martin provided in Dr. Ferrara's October 6, 2004 office record to the effect that he was not using sildenafil at that time. If by "at that time" he was also referring to the second attack of NAION, it is obvious that sildenafil could not be implicated.

13. Fourth, in toxic optic nerve disorders (optic nerve damage from chemical substances such as medications) *both eyes are affected simultaneously.* Kerrison has stated that "Patients who have a toxic optic neuropathy present with a chief complaint of *bilateral loss of vision*" and "The visual acuity loss, dyschromatopsia, and visual fields are typically *bilateral and symmetric.*" (Kerrison, p. 482, 2004). At his initial presentation, Mr. Martin had marked involvement of one eye at a time that the other eye, which was carefully examined, was completely normal. Thus, in the case of Mr. Martin, the visual dysfunction began in one eye before the other and was neither symmetric nor simultaneous.

14. Fifth, in the acute phase of toxic optic neuropathies the optic nerve head is usually normal or is only slightly swollen (Kerrison, 2004). Hemorrhages are not seen. However Mr. Martin's optic head had "considerable swelling and a small hemorrhage" (Letter from Dr. Dan Nichols to Dr. Ferrara dated May 1, 2002; Martin, Weingarden 0002). The presence of the marked swelling and a hemorrhage are consistent with spontaneous NAION and inconsistent with, and further evidence against, a toxic basis for his NAION.

Scientific Studies That Bear Upon Any Relation Between Sildenafil And NAION

15. Because NAION occurs spontaneously in the general population of men who have not taken sildenafil , and because risk factors for NAION overlap with risk factors for erectile dysfunction, there will be cases of spontaneous NAION among men who use Viagra simply by chance. To determine whether there is a scientifically valid relationship between the medication and NAION, it is necessary to consider whether NAION is more prevalent among sildenafil users, whether sildenafil has physiological effects on the optic nerve that could cause NAION, and whether the clinical presentation and course of NAION that occurs among sildenafil users differs from the clinical presentation and course of spontaneous NAION.

16. In making a determination whether or not sildenafil played a role in the causation or precipitation of Mr. Martin's NAION it is important to examine the available epidemiologic and other scientific evidence.

17. Epidemiology has been defined as "The branch of medicine that deals with the study of the causes, distribution, and control of disease in populations" (American Heritage Dictionary of the English language, 2000). Basically, it is the study of epidemics, which are unusual occurrences of a disease in a population. Most epidemics are characterized by a higher than normal incidence of a disorder. This is recognized by comparing the incidence (new cases per year) or prevalence (number of cases at a particular time) of the disorder in a defined population to the known incidence or prevalence of the disease in a similar population. The incidence of NAION has been investigated in the United States and the results indicate that among individuals age 50 or over (the subset of the population at risk for developing NAION) there are between 2.3 and 10.2 new cases each year per 100,000 population. (Hattenhauer, 1997; Johnson,

1994).

18. Has there been an unusually high number of cases of NAION that has followed the introduction of sildenafil? Just such an investigation was conducted in the United Kingdom to learn the incidence of NAION among sildenafil users. They investigated 28,000 patients between 1998 and 2001 (Shakir, 2001; Boshier, 2002; Boshier, 2004). They found only one case in this population. Based upon the occurrence of only one case, the incidence rate is 2.8 per 100,000 per year. Thus the incidence among sildenafil users is the same as in the general population of patients cited above.

19. A second study was conducted in the United States by investigators who used the National Veterans Health Administration's pharmacy and clinical databases (Margo, 2007). They retrospectively reviewed these databases for the years 2004 and 2005 and identified 4,157,357 men of whom 479,489 had been dispensed erectile dysfunction medications that, including sildenafil, inhibit a naturally body chemical called PDE5. The annual incidence of NAION was 5.3/100,000 which is within the range expected in the same age group (see above). The relative risk of NAION in these men (calculated as 1.02 with a 95% confidence interval of 0.92-1.12) was essentially no different than in men who did not take the medication.

20. A third study investigated the impact of the use of sildenafil on the optic nerve by comparing the prevalence of use of sildenafil in a group of patients with NAION to the prevalence of use of sildenafil in a group of individuals of the same gender and about the same age who did not develop NAION. Such a "case-control" investigation was performed (McGwin, 2006) in the United States. The study found no

statistically significant difference in the rate of use of erectile dysfunction medications in the NAION group and the group without optic neuropathies. Statistical significance is the scientific hallmark of a reliable result. A finding that is not statistically significant does not constitute reliable scientific evidence of an association because the finding may be due to chance. The study also has a number of methodological shortcomings as detailed in Dr. Kimmel's expert report, and in a published review by Danesh-Meyer and Levin (Danesh-Meyer, 2007), including misclassification of whether NAION cases were exposed to sildenafil or tadalifil prior to their diagnosis of NAION, the use of sub-group analysis, failure to mask interviewers, small number of subjects and a high proportion of African-Americans (a group with a low risk of NAION) in the control group.

21. As noted previously, one would expect cases of spontaneous NAION among sildenafil users simply by chance since the disorder was well recognized prior to the introduction of sildenafil. Not surprisingly, therefore, there have been some case reports in the medical literature of NAION occurring in men who had used sildenafil. Because case-reports are anecdotal and lack a comparison group, it is not scientifically valid to rely on them to establish causation (see below).

22. The number of men who have used sildenafil is generally estimated as between 23 and 27 million, with the total number of doses perhaps exceeding a billion. However, in personally reviewing the available published medical reports as of this date, I was only able to identify 21 cases of alleged sildenafil or other PDE5 inhibitor associated optic neuropathy. Even if one allows for the possibility of under-reporting it is obvious that sildenafil use has not created an epidemic of NAION. In fact, the number of cases of NAION allegedly related to the use of sildenafil is so low that one

group of authors (Bella, 2006) even questioned if medications like sildenafil might "exert a protective influence on the evolution of NAION". Danish-Meyer and Levin (2007) have stated that "If the incidence of NAION is 2-10/100,000 then one would expect 100-500 cases a year of NAION where there was recent or distant use of a PDE5 inhibitor, even if there was no excess associated with the use of these drugs." While it has not been scientifically established that sildenafil is in fact protective, the low number of case reports is inconsistent with a causal relationship.

23. The issue of a putative causative role for PDE5 inhibitors was first raised in case-reports and case series. Before reviewing the reported cases of PDE5 associated NAION it is important to comment on the reliability of case reports and case series. Evidence-based medicine is the "gold-standard" in current patient care. The keystone of evidence-based medicine is the judicious use of the best available clinical evidence from systematic research. (Sackett, 1996). A Duke University tutorial "Introduction to Evidence-Based Medicine" (WWW.hsl.unc.edu/Services/Tutorials/EBM) includes a discussion of the relative reliability of various types of studies as sources of evidence in making valid evidence-based medical decisions. The tutorial informs the reader that case series and case reports are the least useful sources since as "they are reports of cases and use no control groups with which to report outcomes, they have no statistical validity." In a publication in the Journal of the American Medical Association whose purpose was to educate physicians on the proper use of articles in the medical literature to assess issues of harm from treatment, the authors point out the weakness of case series and case reports as foundations to determine harm. (Levine, 1994). Referring to the shortcomings of case series and case reports they warn "that there are potentially

undesirable consequences when actions are taken in response to weak evidence." The authors then cite as an example an instance in which a useful medication was withdrawn from the market on the basis of case reports of an adverse effect. However, later appropriate comparative studies showed that the medication was safe. Patients were thus deprived of a valuable medication. It is notable that all three of the leading American general ophthalmology journals (*The American Journal of Ophthalmology, The AMA Archives of Ophthalmology and Ophthalmology*) do not accept individual clinical case reports for publication.

24. Notwithstanding the inherent weaknesses of case-reports, including the fact that they cannot establish causation, and the paucity of reports associating PDE5 inhibitors with NAION, I have reviewed the published reports alleging the occurrence of NAION in association with the use of a PDE5 inhibitor. Analysis of the case reports does not suggest an untoward effect of sildenafil. Of the 21 cases, two of the patients described in these reports had not used sildenafil (Bollinger, 2005; Peter, 2005) and in four others the diagnosis was not NAION (Akash, 2005; Gedik, 2006; Su, 2008; Sivaswamy, 2007) Of the 15 remaining cases one patient had suffered an attack of NAION *prior* to using sildenafil and the authors could not establish "when his visual symptoms began, with respect to the use of sildenafil" (Pomeranz, re: Case # 4, 2002). In two patients described in these reports the interval between taking the medication and the onset of their NAION was too long for the sildenafil to have played any role.(Pomeranz, re: Case #5, 2005).

25. A consideration that is sometimes used to help assess whether a drug has caused a particular side-effect is if there is good evidence that after taking that drug a

second time after it has been discontinued for a period, the side effect recurs. This is referred to as rechallenge. I am aware of two publications that allege to document a positive rechallenge in medications used to treat erectile dysfunction (PDE5 inhibitors). One of these publications (Bollinger, 2005) describes the case of a man who noticed a defect in the lower field of vision in one eye on four consecutive occasions after taking tadalafil. Each time it vanished spontaneously within 24 hours. The fifth time he ingested the drug the field defect developed but did not clear. He was not examined until 14 days later when there was evidence in that eye of NAION. First it must be noted that he did not take sildenafil. He took a related drug used for the treatment of erectile dysfunction and there can be critical differences in toxicity between drugs that are closely related chemically. An example is the anti-tuberculosis drug ethambutol which has been shown to damage the optic nerve. The drug originally contained two variations (stereo-isomers) of the same chemical, differing merely in that the molecular structure of one was the mirror image of the other. Nevertheless, one was quite toxic to the visual pathways and had little anti-tuberculous effect, while its mirror image had little toxicity at customary doses and was a potent anti-tuberculous agent. (Spencer, p. 603,1980). More pertinent is the observation that the transient retinal symptoms that may occur with the use of PDE 5 inhibitors that result from cross-reactivity with PDE-6 inhibition, are less likely to occur with tadalafil than with sildenafil. (Bella, 2006). Thus, one cannot assume that a side-effect allegedly resulting from the ingestion of tadalafil could also occur with sildenafil. In any case, premonitory symptoms such as those described by that patient, are encountered in spontaneous NAION. Furthermore rechallenge means that the disorder recurred and the tadalafil patient had only one

documented episode of NAION. Thus, this case does not represent proof of a positive rechallenge response.

26. A second publication alleging a positive rechallenge response (Pepin, 2008) describes the case of a man who used sildenafil "sporadically" for 5 years without incident. Then he ingested the medication (time not supplied) and the next day (the interval is not supplied) he had an inferior field defect left eye. Examination 17 days later showed signs of NAION. Over the next 2 weeks he took sildenafil twice more and each time "within 24 hours" (again the exact details are not provided) his visual field defect worsened. I infer that examinations were not performed each time to establish that changes had indeed occurred. It is by no means unusual for patients with spontaneous NAION to worsen over weeks following the initial loss of vision. In fact the authors cite a publication that reports this common progression (Hayreh and Zimmerman, 2008) and they state that "the visual loss in NAION can expand spontaneously over several weeks after initial symptoms." Thus, the evidence for a positive rechallenge response in this case is weak. Furthermore, the patient stopped the sildenafil and yet failed to improve. It should be noted that dechallenge (improvement after stopping a drug) is also a criterion that is sometimes used to assess whether a drug is toxic. In the patient described in the publication by Pepin and Pitha-Rowe the dechallenge was negative (negative dechallenge).

27. In light of the foregoing, it is not surprising that the United States Food and Drug Administration (FDA) and the World Health Organization (WHO) have concluded that there is at present a lack of conclusive evidence of a causal relation between the use of erectile dysfunction drugs such as sildenafil and the risk of NAION.

(Danesh-Meyer, 2007). The World Health Organization has listed sildenafil as neither "certain" nor "probable" as a cause of anterior ischemic optic neuropathy (Santaella, p. 79, Table II, 2007).

28. Thus, there is no epidemiological evidence showing a link between use of sildenafil and NAION.

29. There have been scientific investigations regarding the effect of sildenafil on ocular blood flow. NAION is by definition a disorder in which the damage to the optic nerve presumably results from impairment of blood supply to the region of the optic nerve head. Is there scientific evidence that bears upon the effects of sildenafil ingestion on the blood supply of the optic nerve head and adjacent regions? If sildenafil causes or contributes to the occurrence of NAION one would expect that the ingestion of that medication would negatively impact the blood supply to the region of the optic nerve head. One would be particularly interested in the effect of sildenafil on the posterior ciliary and ophthalmic arteries since they convey the blood that supplies the region of the optic nerve head and also the effect of sildenafil on the vessels of the choroid, a structure that shares some of its blood supply with the adjacent optic nerve. One pertinent investigation (Paris, 2001) tested the right eyes of twelve normal human subjects before, and two hours after, ingesting sildenafil using two methods of testing the responses of the vasculature; pulsatile ocular blood flow and retinal flowmetry. They also measured intraocular pressure and systemic blood pressure, and performed a test of visual function (contrast sensitivity). There was a significant increase (29.4%) in pulsatile ocular blood flow without alteration in any other measures of pressure or flow. Interestingly the subjects demonstrated a significant (33.6%) improvement in contrast sensitivity. Not

only do these results fail to show that sildenafil impairs circulation (or visual function), but they also show that there is evidence of increased flow and even improved visual function. Furthermore they even suggested that in light of the salutary effect of ingesting sildenafil, there might be a role for the drug in the *treatment* of visual disorders. In a review article by Harris et al (Harris, 2008) 13 publications describing the effects of sildenafil on the vasculature of the human eye are cited and critiqued. Six of those cited publications (Foresta, 2008; Sponsel, 2000; Grunwald, 2001; Dundar, 2001; Koksal, 2005; Metelitsina, 2005) described the results of investigations of blood flow in the pertinent structures mentioned above. In four of the investigations there was an *increase* in flow and in the remainder *no difference* between the resting state or the use of a placebo and following administration of sildenafil was observed. Harris et al (page 473) concluded that "[t]he current studies on ocular blood flow therefore do not support a blood-flow-related mechanism connecting NAION to PDE5 inhibitors." Based on my independent review of the studies, I agree.

30. As Fraunfelder, Pomeranz and Egan concluded in their editorial "Nonarteritic Anterior Ischemic Optic Neuropathy and Sildenafil" (2006) "a well-researched explanation as to how sildenafil could cause NAION does not exist". It is notable that Lloyd and Fraunfelder (2007) in their Table "Drugs With Known Adverse Effects on the Optic Nerve" (see Table 1, pp. 828-829) which has over 200 entries, failed to include sildenafil.

Plaintiffs' Expert Reports

31. I have reviewed the report submitted by plaintiffs' experts and find them flawed as discussed below.

Andrew Go Lee, MD

32. In his first paragraph Dr. Lee glosses over the fact that Mr. Martin had taken numerous doses of sildenafil without ill-effect for 4 years prior to the development of NAION. This is inconsistent with the notion that Mr. Martin represents an example of a positive challenge-rechallenge case. It is inappropriate methodology to ignore Mr. Martin's prior extensive experience with the medication.

33. Dr. Lee writes that Mr. Martin had testified that he had taken sildenafil the evening prior to each episode of NAION. Actually the interval between Mr. Martin's last use of sildenafil and the onset of his visual impairment is uncertain. Depending upon which testimony one accepts, Mr. Martin's first attack occurred either when he was not exposed to sildenafil (see Dr. Ferrera's medical records dated October 6, 2004: MARTIN, R FERRERA 0092), or about 24 hours after using it (see Mr. Martin's deposition testimony page 168, lines 16-21). In the former case it is obvious that sildenafil could not have played a role. Even in the latter case, in view of the short half-life of the medication, sildenafil would have been metabolized (degraded by chemical processes in the liver) and no longer present in Mr. Martin's system. In regard to the attack of NAION in his second eye, Mr. Martin in his deposition (pages 172-176) testified that he took the sildenafil around 7-8 PM and that the visual loss occurred at dusk the next day. Even accepting that testimony at face value, the interval, which I estimate to be no less than 22 hours is, again, such that the sildenafil would have been absent from his body or (less likely) present in such a tiny concentration as to be inconsequential. However, there is also the information that Mr. Martin provided in Dr. Ferrara's October 6, 2004 office record to the effect that he was not using sildenafil at that time. If by "at that time" he was also referring to the second attack of NAION, it is

obvious that sildenafil could not be implicated. It is inappropriate for Dr. Lee to overlook the specific details of how much time elapsed between Mr. Martin's use of sildenafil (if he in-fact used the medication) and the onset of visual loss. It is obvious in light of the information on timing and use of sildenafil provided in testimony by Mr. Martin and in testimony by, and the office records of, Dr. Ferrera that Mr. Martin had either no plasma concentration or negligible plasma concentrations of sildenafil when his visual symptoms developed. Dr. Lee has no foundation for his citing the temporal relation in support of his opinion that "...the use of sildenafil was a significant precipitating factor for bilateral rapidly sequential NAION."

34. Dr.Lee also cites the nocturnal use of the drug as a factor in reaching his opinion but fails to state why this is significant. Dr. Lee also cites the short interval between episodes of NAION as supporting his opinion. However as Hayreh and his co-authors have written: involvement of the second eye is a common occurrence in patients with NAION and the attacks in the two eyes can occur "days, months or even years apart." (Beri, 1987). Based on data from the Ischemic Optic Neuropathy Decompression Trial (Newman, 2002), and in my own experience, it is clear that spontaneous NAION can affect the two eyes after intervals as short as weeks.

35. Dr. Lee states that another reason for his opinion is that there is a biologically "plausible" mechanism for the effect but he fails to indicate what that is. It is accepted that the pathophysiology of NAION is unknown (Lessell, 1999; Levin, 2008). My review of the scientific literature and reviews by others have failed to show that there is any scientific evidence for a mechanism underlying NAION caused by sildenafil.

36. Dr. Lee states that there were no alternative etiologies. However, he

ignores the fact that, by definition, spontaneous NAION is a disorder in which there is no evident alternative etiology, as Dr. Lee himself noted in an article that he co-authored. Lee, 2005). Therefore the absence of an alternative etiology is not a reason to implicate sildenafil in Mr. Martin's NAION.

37. Dr. Lee next mentions Mr. Martin's "predisposing vasculopathic risk factors". As I discussed above those very risk factors are themselves sufficient to explain the occurrence of *spontaneous* NAION in Mr. Martin.

38. Finally Dr. Lee alleges that Mr. Martin demonstrated a positive rechallenge. First I would remind the reader that Mr. Martin had hundreds of rechallenges prior to April 30, 2002 and never developed any vision problems. As for the "rechallenge" in the late spring of 2002, the lack of detailed information about whether or when he was using sildenafil makes it impossible to determine whether there had been a positive rechallenge.

39. Dr. Lee's opinion that in the case of Mr. Martin "the use of sildenafil was a significant precipitating factor for bilateral rapidly sequential NAION" is inconsistent with his written article (Lee, 2005) where he states the following: "Although the case reports to date suggest a *possible* association between NAION and PDE5-5 inhibitors, *a causal relationship has not been established conclusively*" (italics mine); "Thus a certain number (several hundred to perhaps a few thousand) of spontaneous NAION events would be expected to occur each year in a population of 23 million older age men using sildenafil. *Some of these events (depending on the frequency of use of the drug) would fall by chance alone within six to 36 hours of taking sildenafil*" (italics mine); "Recollection, selection, and ascertainment bias might also be at play among the

retrospective cases reported to date".

Neal Sher, MD

40. In his "History Of Present Problem" Dr. Sher does not provide detailed information regarding the interval between Mr. Martin's alleged use of sildenafil and the onset of the visual impairment on either of the occasions when he developed NAION. This information is critical because the amount of sildenafil remaining in the bloodstream (plasma concentration) is very low 12 hours after the medication has been taken, even in patients 65 years of age or older (Physicians' Desk Reference, p. 2562, 2008).The length-of-time between Mr. Martin's last use of sildenafil and the onset of his visual impairment is actually uncertain. Depending upon which testimony one accepts, Mr. Martin's first attack occurred either when he was not exposed to sildenafil (see Dr. Ferrera's medical records dated October 6, 2004: MARTIN, R FERRERA 0092), or about 24 hours after using it (see Mr. Martin's deposition testimony page 168, lines 16-21). In the former case it is obvious that sildenafil could not have played a role. Even in the latter case, in view of the short half-life of the medication, sildenafil would have been metabolized (degraded by chemical processes in the liver) and no longer present in Mr. Martin's system. In regard to the attack of NAION in his second eye, Mr. Martin in his deposition (pages 172-176) testified that he took the sildenafil around 7-8 PM and that the visual loss occurred at dusk the next day. Even accepting that testimony at face value, the interval, which I estimate to be no less than 22 hours is, again, such that the sildenafil would have been absent from his body or (less likely) present in such a tiny concentration as to be inconsequential. However, there is also the information that Mr. Martin provided in Dr. Ferrara's October 6, 2004 office record to the effect that he was not using sildenafil at that time. If by "at that time" he was also

referring to the second attack of NAION, it is obvious that sildenafil could not be implicated. Thus Dr. Sher fails to recognize the importance of knowing exactly how much time had elapsed between Mr. Martin's use of sildenafil (if he in-fact used the medication) and the onset of visual loss. In fact with regard to the second episode of NAION he states that Mr. Martin noticed his loss of vision in the morning but there is no evidence to support that in any of the medical records or deposition testimony. It is obvious in light of the information on timing and use of sildenafil provided in testimony by Mr. Martin and in testimony by, and the office records of, Dr. Ferrera that Mr. Martin had either no plasma concentration or negligible plasma concentrations of sildenafil when his visual symptoms developed. Despite this, Dr. Sher specifies in the "Discussion" section of his report that his opinion that Mr. Martin's visual loss resulted from sildenafil is based upon, among other things, the "temporal relationship of Sildenafil use."

41. In his "Discussion" section Dr. Sher states that his opinion implicating sildenafil in Mr. Martin's case is also based upon "...the clinical findings of Mr. Martin's case." In fact, the clinical findings in Mr. Martin's case are no different from those in cases of spontaneous NAION. The ophthalmologist (Dr. Dan Nichols) and the neuro-ophthalmologist (Dr. Andrew Harrison) who examined and evaluated Mr. Martin at the time of his visual loss (see Dr. Sher's report under "History Of Present Problem") both considered that Mr. Martin had NAION and did not observe features that would make the clinical findings different from spontaneous NAION.

42. Dr. Sher abstracts portions of an editorial on a possible relation of sildenafil use to NAION by Dr. Hayreh (Hayreh, 2008) to support his contention that Mr. Martin's NAION was related to his use of sildenafil. One factor he mentions is the

temporal relation of medication use to the loss of vision. As noted above, that could not be a valid factor in Mr. Martin's case owing to his either not having used sildenafil at the time of the onset of NAION, or having used it so long before that the plasma concentration would be at most negligible. Dr. Hayreh next uses the presence of "predisposing factors such as small vessel disease". Of course this is no different from spontaneous NAION in which a drug effect is not required to cause the problem (Ischemic Optic Neuropathy Decompression Trial Study Group, 1996). The third element of Dr. Hayreh's article invoked by Dr. Sher is the speculation that "*Possible* hypotension...localized to the optic nerve from the combined use of the PDE5 inhibitors, alpha and beta blockers" is a factor in causing NAION (italics mine). This is not supported by scientific evidence and remains mere speculation. (The report of plaintiffs' other expert, John M. Williams, Sr M.D., MPH, relies on Dr. Hayreh's editorial for his causation opinion, and is flawed for the same reasons).

43. Dr. Sher then mentions a recent publication (Levin, 2008) which sets forth a new "Hypothesis" for the pathogenesis of NAION. Note that this is by the authors' admission a "hypothesis" which is defined as "An assumption or concession made for the sake of argument."(Merriam-Webster's Collegiate Dictionary, 2007). The definition goes on to state "hypothesis implies insufficient evidence to provide more than a tentative explanation". In any case these authors (citing Lessell,1999) acknowledge that the pathophysiology of NAION is unknown. They suggest that the mechanism of NAION, spontaneous or otherwise, might be from congestion within the anterior optic nerve owing to impaired venous drainage perhaps associated with, or initiated by, arterial dilatation. They postulate that there is a "compartment syndrome" leading to damage to

the optic nerve. A compartment syndrome is the compression of nerves and blood vessels within an enclosed space. In the anterior optic nerve there is only one small area in which the nerve is confined by the adjacent rigid tissue (the sclera) but that only restricts the sides of the nerve. The space is not truly enclosed as the nerve is free to expand towards the eye. The existence of a compartment syndrome in NAION has never been demonstrated and remains hypothetical. They speculate that PDE5 inhibitor use (mentioned as a "possible association" and which they state is a "controversial association") could cause NAION by their proposed mechanism. Presumably in support of the association of PDE5 inhibitors and NAION they cite a case report of "multiple rechallenge episodes." (Bollinger, 2005). The single patient described in that case report did not take sildenafil. Instead he used another drug used for the treatment of erectile dysfunction and it should be emphasized that there can be critical differences in toxicity between drugs that are closely related chemically to each other. An example is the anti-tuberculosis drug ethambutol which has been shown to damage the optic nerve. The drug originally contained two variations (stereo-isomers) of the same chemical, differing merely in that the molecular structure of one was the mirror image of the other. Nevertheless, one was quite toxic to the visual pathways and had little anti-tuberculosis effect, while its mirror image had little toxicity at customary doses and was a potent anti-tuberculosis agent. (Spencer, p. 603, 1980). More pertinent is the observation that the transient retinal symptoms associated with the use of PDE 5 inhibitors in the treatment of erectile dysfunction that result from cross-reactivity with PDE-6 inhibition, are less likely to occur with tadalafil than with sildenafil. (Bella, 2006). Thus, absent empirical scientific evidence (which is not present here), one cannot assume that a

side-effect allegedly resulting from the ingestion of tadalafil could also occur with sildenafil. In any case, premonitory symptoms such as those described by that patient are encountered in spontaneous NAION. Furthermore rechallenge means that the disorder recurred and since the tadalafil patient had only one documented episode of NAION, this case does not represent proof of a positive rechallenge response.

44. The venous hypothesis of Levin and Danesh-Meyer remains by their own admission merely a hypothesis and the events that they have postulated as occurring in the anterior optic nerve to cause NAION, spontaneous or otherwise, have never been scientifically documented or even tested.

45. Finally Dr. Sher cites McGwin (McGwin, 2006) as the the "most convincing epidemiologic study of the association between ED treatment and NAION." In fact that study found no statistically significant difference in the rate of use of erectile dysfunction medications in the NAION group and the group without optic neuropathies. Statistical significance is the scientific hallmark of a reliable result. A finding that is not statistically significant does not constitute reliable scientific evidence of an association because the finding may be due to chance. The study also has methodological shortcomings as detailed in Dr. Kimmel's expert report and in a published review by Danesh-Meyer and Levin (2007).

Gerald McGwin, MS, PhD

46. On page 2, second paragraph Dr. McGwin implies that "well documented visual side effects" (light sensitivity and color vision abnormalities) of sildenafil adds to the plausibility that sildenafil is associated with an increased risk of NAION. However, since the visual side effects that he cites are of retinal origin and not those that one finds in NAION, and are transient, adds nothing to the "plausibility" that sildenafil is

associated with an increased risk of NAION because these conditions are not associated with NAION and result from transient effects on the retina, not the optic nerve. He also contends that hypoperfusion occurs as a consequence of sildenafil use. On the contrary no investigations have documented hypoperfusion and most have shown hyper-perfusion. The hypotensive effect of sildenafil to which he refers is, as he admits, "mild" and he is offering nothing more than unfounded speculation about a role of hypotension. The last sentence of the paragraph concerning a compartment syndrome also lacks a scientific foundation since the occurrence of a compartment syndrome is merely a hypothetical construct (Danesh-Meyer, 2007).

47. On page 4, item IV. He indicates that sildenafil can cause "other ocular vascular disorders". There have been rare case reports of individuals who have sustained other ocular vascular disorders allegedly in association with the use of sildenafil. However, these are mere case reports without a comparison group and it is improper methodology to rely on such case reports to establish a causal link.

48. Item V. Dr. McGwin discusses rechallenge and dechallenge case reports. As detailed above, there are no cases of dechallenge or positive rechallenge in sildenafil users. Importantly Dr. McGwin fails to mention that the FDA reviewed case reports including those that involved alleged challenge or rechallenge and concluded that the evidence was insufficient to establish causation.

49. Page 5 Dr. McGwin's implication that the interval between the episodes in Mr. Martin's case take it out of the realm of spontaneous NAION is refuted by the medical literature and by my own experience, as discussed above. Furthermore, contrary to what Dr. McGwin states it is not clear when (or if) Mr. Martin used sildenafil.

Even if we accept Dr. McGwin's position that there was a 24 hour interval between ingesting sildenafil and developing NAION, the drug could not be blamed owing to the fact that by 24 hours all of the sildenafil would have been metabolized and not present in his blood plasma.

Conclusion

50. Based upon my review of Mr. Martin's medical history and my review of the results of epidemiological and other scientific studies in the medical literature described above, it is my opinion to a reasonable degree of medical certainty that sildenafil use did not cause or contribute to Mr. Martin's non-arteritic anterior ischemic optic neuropathy (NAION).

My hourly fee for work in this matter is $800. A schedule of my prior trial and deposition testimony in the past four years to the best of my recollection is attached.

Dated: December 19,2008

Sigmons Lessell, MD

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Schedule of Trial and Deposition Testimony

To the best of my recollection, in the past four years, I have testified at deposition or at trial in the matters listed below:

Trial Testimony

- In Chester, PA for plaintiff vs an ophthalmologist who failed to recognize that the plaintiff had a visual field defect as a result of a stroke.
- In Cincinnati, OH for plaintiff vs an ophthalmologist who neglected post-operative glaucoma resulting in blindness.
- In Minneapolis MN for plaintiff DeHaan.vs Mayo Clinic for ischemic optic neuropathy after massive hemorrhage during surgery that was not corrected adequately by the physicians.

Deposition Testimony

- In Boston, MA for defendant cardiologist in Georgia who was accused of causing ischemic optic neuropathy by prescribing amiodarone.
- In Boston MA for plaintiff vs an ear-nose-throat surgeon in Oklahoma who was accused of damaging a patient's optic nerve in the course of sinus surgery.
- In Boston MA for defendant trucking company in Georgia regarding nature of employee's injury and relation to his blinding disorder of the optic nerve (Leber's hereditary optic neuropathy).

CURRICULUM VITAE

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Date of Birth May 25, 1933
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B.A. Cum Laude	Amherst College	1954
M.D.	Cornell University Medical College	1958
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Intern – Medicine	Second (Cornell) Medical Division Bellevue Hospital, New York, New York 1958 - 1959
Resident – Neurology	University of Vermont Affiliated Hospitals Burlington, Vermont 1959 – 1960
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Archives of Ophthalmology
Journal of Neuro-ophthalmology

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American Medical Association
Massachusetts Medical Society (Middlesex – South District)
New England Ophthalmological Society
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PUBLICATIONS

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